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## A Case of Lactic Acidosis Caused by Stavudine in an AIDS Patient

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Nucleoside reverse transcriptase inhibitors (NRTIs), which are used for the treatment of human immunodeficiency virus (HIV) infection have been associated with a wide spectrum of clinical manifestations, including hepatic steatosis, lipodystrophy, myopathy, and lactic acidosis. Such adverse effects are postulated to result from the inhibition of mitochondrial DNA gamma polymerase, which causes the depletion of mitochondrial DNA and eventual the disruption of oxidative phosphorylation. Although cases of severe decompensated lactic acidosis are rare, this syndrome is associated with a high mortality rate. We report upon the first Korean case, of severe lactic acidosis in an acquired immunodeficiency syndrome (AIDS) patient receiving stavudine, an anti- HIV drug.

**Key Words :** Lactic acidosis, Stavudine, HIV, Anti-HIV Drugs, Acquired Immunodeficiency Syndrome

### INTRODUCTION

Highly active antiretroviral therapy (HAART) enhances the immune state of immunodeficiency virus (HIV) infected patients, by suppressing the replication of HIV. This enhancement in the immune state reduces the risk of opportunistic infections, and thus HAART has improved the survival and quality of life of AIDS patients, and now plays a central role in the treatment of HIV infection<sup>1)</sup>. Nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) are widely used for HAART<sup>1)</sup>. It has also been reported that when antiretroviral drugs, especially NRTIs are administered, that they may cause lipodystrophy syndrome due to the abnormal accumulation or diminution of lipid, dyslipidemia, lactic acidosis or even an abnormal glucose metabolism<sup>2)</sup>. Lactic acidosis, in particular, is a life threatening adverse effect, and has been associated with almost all NRTIs, e.g., with zidovudine (AZT) or didanosine (ddl)<sup>3, 4)</sup>. According to recent reports, many cases of lactic acidosis have been attributed to Stavudine (d4T)<sup>5-7)</sup>. However, no case of lactic

acidosis has been reported in Korea. We present a case of severe lactic acidosis caused by stavudine and include a review of the literature.

### CASE REPORT

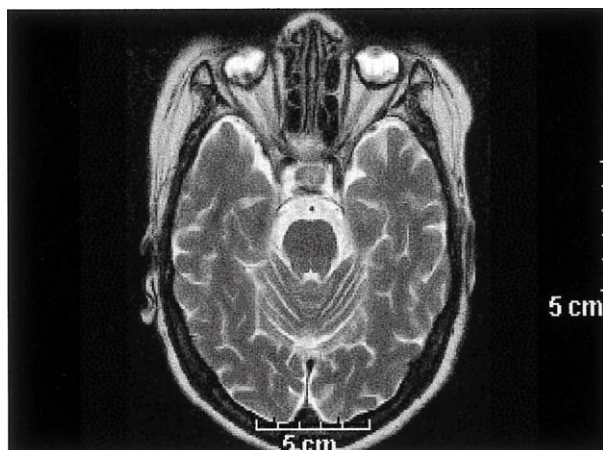
A 44-year-old woman was admitted to the hospital because of nausea, vomiting and paraplegia of both lower extremities. She was diagnosed as HIV positive in June, 2000, when she presented with retinal necrosis caused by the varicella zoster virus. Subsequently, she was started on zidovudine, lamivudine, and indinavir at a baseline CD4 positive T lymphocyte count of 16/ $\mu$ L, a CD8 positive T lymphocyte count of 86/ $\mu$ L and a HIV-RNA of 1,129,768 copies/mL. Subsequently, medication was changed to lamivudine, stavudine, lopinavir/ritonavir in April, 2002 due to leukopenia caused by the zidovudine. She remained on this medication for 8 months, prior to December 2002, when she stopped the medication 10 days before admission due to the symptoms mentioned above. In January

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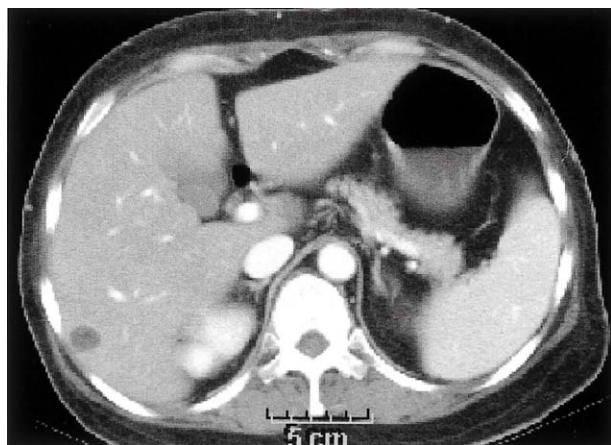
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2000, the patient was diagnosed with chronic viral hepatitis B. She had no history of hypertension, tuberculosis or DM, and no medication other than antiretroviral drugs had been taken. On admission, the patient complained of general weakness, nausea, vomiting and paralysis of both lower extremities. However, she did not present fever, chills, abdominal pain, constipation or diarrhea. The patient's blood pressure was 110/80 mmHg, pulse rate 80/min, respiration rate 25/min, temperature 36°C. She had a chronically ill-looking appearance and an alert mental status. Conjunctivae were not pale, sclerae were not icteric and cervical lymph nodes were not palpable. On chest auscultation, breathing sounds were clear in both lungs; her heartbeat was regular without murmur. The Abdomen was soft and flat without tenderness, and bowel sounds were normoactive. The liver and spleen were not palpable and



**Figure 1.** Brain MRI, showing no abnormal signal intensity or abnormal mass lesion in T2WI. The ventricular system was within normal limits.



**Figure 2.** Abdominal-pelvic CT showing small cysts in the liver. No grossly visible mass or lymphadenopathy was present.

no palpable abdominal mass was found by physical examination. Muscle strength of both legs had decreased to Gill, and there were no deep tendon reflexes (DTRs). Neither CVA tenderness nor pitting edema of the extremities was apparent. A laboratory examination showed a WBC of  $6,920/\text{mm}^3$  (neutrophils 58.8%, lymphocytes 29.1%, monocytes 6.9%, eosinophils 1.3%), a Hb of 14.7 mg/dL, a hematocrit of 42.3%, and a platelet count of  $159,000/\text{mm}^3$ . Blood chemistry revealed: calcium 9.5 mg/dL, inorganic P 0.4 mg/dL, uric acid 14 mg/dL, ALP 71 IU/L, amylase 48 IU/L, lipase 111 IU/L, BUN 6.8 mg/dL, Creatinine 0.8 mg/dL, total protein 7.0 g/dL, albumin 4.7 g/dL, AST/ALT 71/60 IU/L, total bilirubin 2.7 mg/dL, direct bilirubin 1.7 mg/dL, Na/K/Cl/tCO<sub>2</sub> 135/3.1/95/8 mEq/L, total cholesterol 252 mg/dL, TG 305 mg/dL, HDL-cholesterol 16 mg/dL, LDL cholesterol 157 mg/dL, lactate 10.8 mmol/L (normal 0.5–1.6 mmol/L), and creatinine kinase 3 IU/L. Immunochemistry showed positive HBeAg, HBV DNA 1,321 pg/mL, AFP 10.61 IU/mL (normal 0–7 IU/mL), and CEA 0.566 ng/mL (normal 0–5 ng/mL). The CD4 positive T lymphocyte count was  $117/\mu\text{L}$ , the CD8 positive lymphocyte count  $687/\mu\text{L}$ , and a HIV-RNA level of 133,000 copies/mL. Her pregnancy test was negative, as were blood, urine and stool culture. A cerebrospinal fluid examination performed to rule out a central nervous system infection showed no significant findings, and neither did brain MRI (Figure 1). A contrast CT scan of the abdomen, performed to rule out intra-abdominal malignancy, showed only a hepatic cyst (Figure 2). Arterial blood gas analysis (ABGA) revealed a pH of 7.291, pCO<sub>2</sub> 12.6 mmHg, pO<sub>2</sub> 142.1 mmHg, SaO<sub>2</sub> 99%, and BE-ECF 20.6. Accordingly, a diagnosis of lactic acidosis was made. Intravenous sodium bicarbonate infusion and conservative treatment were immediately initiated and antiretroviral drugs were stopped. The symptoms of nausea and vomiting subsided on the third day of treatment and from the tenth day, her paraplegia of both legs also started to improve. ABGA results and lactate levels gradually normalized (Table 1) and on the 11<sup>th</sup> day, ABGA showed pH 7.474, pCO<sub>2</sub> 39.9 mmHg, pO<sub>2</sub> 79 mmHg, SaO<sub>2</sub> 96.3%, BE-ECF +5.8, and lactate 2.9 mmol/L. The patient was discharged on the 14<sup>th</sup> day without any signs of lactic acidosis. At the time of discharge, total bilirubin had decreased to 1.3 mg/dL. After discharge, antiretroviral medications were resumed in the order:- of

**Table 1.** Serial arterial blood gas analyses and lactate concentrations after sodium bicarbonate infusion and discontinuation of stavudine

Hospital day	1 day	2 day	5 day	11 day
pH	7.29	7.432	7.351	7.474
pCO <sub>2</sub> (mmHg)	12.6	18.4	36.4	39.9
BE-ECF	-20.6	-12.1	-5.5	+5.8
Lactate (mmol/L)	10.8	6.0	3.7	2.9

lamivudine, efavirenz, and lopinavir/ritonavir; none of the previous symptoms recurred. Two months after discharge, her serum lactate level was 4.8 mmol/L. The patient is still on antiretroviral therapy and is being followed up on an outpatient basis.

## DISCUSSION

HAART serves a major role in the treatment of HIV infection. Therapy is considered if the patient is symptomatic or when the CD4 positive T lymphocyte  $<350/\mu\text{L}$  or HIV-RNA  $>$  exceeds 55,000 copies/mL in non-symptomatic patients<sup>1</sup>. For initial therapy, two NRTIs are usually used in combination with PIs or NNRTIs<sup>1</sup>. NRTIs suppress HIV reverse transcriptase, which, inhibits viral DNA synthesis. However, these drugs induce severe complications by also suppressing DNA synthesis by mitochondrial polymerase- $\gamma$ <sup>2</sup>. Zidovudine, the first NRTI used in HIV treatment, can cause hepatic steatosis, lactic acidosis and even myopathy<sup>3</sup>. Didanosine is also reported to cause adverse effects, such as acute pancreatitis, in addition to those caused by zidovudine<sup>5, 6</sup>. Stavudine, a derivative of thymidine, which was the fourth NRTI to be used in this case, may cause peripheral neuropathy<sup>5, 6</sup>, lactic acidosis<sup>7</sup>, cardiomyopathy<sup>8</sup>, pancreatitis<sup>1</sup> and Guillain-Barre syndrome<sup>5</sup>. These complications occur due to the depletion of mitochondrial DNA caused by the suppression of DNA polymerase- $\gamma$ , followed by dysfunction of cellular oxidative phosphorylation<sup>9</sup>. In contrast, NNRTIs and PIs have not been reported to cause such adverse effects of mitochondrial toxicity, which is attributed to their selectivity for HIV reverse transcriptase<sup>1</sup>. The most common complication of NNRTIs is skin eruption, other include PIs, hyperglycemia and dyslipidemia<sup>1, 2</sup>. Lactate is the final product of glycolysis, which in a normal state does not accumulate in the body. However, under circumstances such as oxygen deprivation of tissue or impaired oxidative phosphorylation, hyperlactatemia occurs. Lactic acidosis is defined as a serum lactate level  $>5$  mmol/L accompanied by metabolic acidosis<sup>10</sup>. Since 1991, when acute hepatic failure and lactic acidosis was first reported to be caused by didanosine<sup>11</sup>, lactic acidosis by NRTIs has been considered as a rare, but fatal complication. The symptoms of lactic acidosis are typically nonspecific, but include fatigue, abdominal pain, vomiting, and weight loss. When such symptoms are accompanied by dyspnea on exertion, it is mandatory that serum lactate levels be measured. The presence of tachycardia at a normal body temperature is highly suggestive of lactic acidosis<sup>12</sup>. Since most HIV infected patients are admitted to hospital with such nonspecific symptoms, it is easy to neglect lactic acidosis. Although earlier reports have been issued on lactic acidosis due to

zidovudine or didanosine<sup>3, 4)</sup>, stavudine is frequently the more recent reported cause<sup>5-7)</sup>. Since cases of fatal lactic acidosis caused by stavudine and didanosine in pregnant women have been reported, the administration of these drugs during pregnancy is now considered with a high degree of caution<sup>19, 20)</sup>. Luzzati et al.<sup>20)</sup> postulated a high possibility of mitochondrial toxicity due to NRTIs in pregnant women, because the riboflavin concentration runs low during pregnancy. Risk factors of lactic acidosis, other than pregnancy, include female sex, obesity and the duration of NRTI therapy<sup>1)</sup>. Moreover, it is important that lactic acidosis be distinguished from asymptomatic hyperlactatemia. John et al.<sup>13)</sup> reported that the majority of HIV-positive patients taking NRTIs developed chronic asymptomatic hyperlactatemia; their average serum lactate concentration was reported to be 1.5~3.5 mmol/L. The administration of and the duration of exposure to stavudine are reported to be major risk factors of hyperlactatemia<sup>13)</sup> and PIs or NNRTIs were not found to meaningfully affect the development of hyperlactatemia. However, a minority of hyperlactatemia patients eventually developed lactic acidosis. According to Boubaker et al.<sup>14)</sup> a significantly higher incidence of hyperlactatemia was observed in a group of patients treated with stavudine, and no apparent relationship was found between age, gender, CD4 positive T lymphocyte count and the development of hyperlactatemia. Furthermore, in many cases, lipodystrophy, dyslipidemia, and hyperglycemia were accompanied with hyperlactatemia. According to the report of Yann et al.<sup>12)</sup>, the annual incidences of hyperlactatemia were 0.8% and 1.2% in NRTIs or stavudine administered AIDS patient groups, respectively. Coghlan et al.<sup>16)</sup> reported in their retrospective study of HIV positive patients with lactic acidosis that the majority of patients took stavudine and didanosine. Lactic acidosis is accompanied by myopathy, lipodystrophy, fulminant hepatic failure, and pancreatitis in many cases<sup>1, 2)</sup>. And, stavudine is reported to cause Guillain-Barre syndrome<sup>5)</sup> demonstrating that NRTIs damage multiple organs by depleting mitochondrial DNA. Treatments for lactic acidosis include; the immediate discontinuation of medication, conservative treatment and the correction of the acidosis. Dalton et al.<sup>17)</sup> and Yann et al.<sup>18)</sup> reported upon the successful treatment of lactic acidosis with riboflavin and L-carnitine, but the effect of this treatment is as unproven. The discontinuation of medication corrects most cases of hyperlactatemia, but the continuation of hyperlactatemia for 176 days has been reported<sup>2, 15)</sup>. Because our patient had no other causes of lactic acidosis (infection, shock, malignancy, ischemia or cirrhosis) and did not take any medication other than the anti-retroviral drugs, the lactic acidosis was ascribed to the NRTI. Considering that her lactic acidosis developed while she had been taking stavudine, and that the lactic acidosis did not recur while stavudine alone was replaced by efavirenz, a NNRTI, stavudine appears to have been the

culprit. Since the total bilirubin level of the patient upon presentation was elevated to twice the normal value, it was likely that she had hepatic steatosis. After conservative treatment, however, the bilirubin level recovered to the norm, and so a liver biopsy was not performed. Therefore, we could not entirely exclude the possibility of hepatotoxicity due to lopinavir/ritonavir. The following characteristics of the paraplegic symptoms were noted: First, a symmetric and rapid development. Secondly DTRs was lost upon neurological examination. Third no predisposing infection preceded, and fourth, the symptoms fully disappeared in two months. According to these findings, the most likely diagnosis is Guillain-Barre syndrome. Although stavudine is suspected to be the likely cause of this Guillain-Barre syndrome in view of the accompanying lactic acidosis; however, we could not confirm stavudine as the cause due to the lack of a nerve conduction velocity test.

## SUMMARY

NRTI, used in HAART, suppresses mitochondrial DNA polymerase- $\gamma$  driven DNA synthesis. Thus, it could possibly cause serious adverse effects, such as lactic acidosis, hepatic steatosis and myopathy. Because we experienced this case of lactic acidosis during the administration of stavudine in an AIDS patient, and this was followed by a subsequent successful treatment, we report this case and include a review of the literature.

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